

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 January 2001 (18.01.01)
International application No. PCT/US00/15069
International filing date (day/month/year) 31 May 2000 (31.05.00)
Applicant AUGELLI-SZAFRAN, Corinne, Elizabeth et al

Applicant's or agent's file reference  
5944-01-TMC

Priority date (day/month/year)  
10 June 1999 (10.06.99)

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

09 December 2000 (09.12.00)

in a notice effecting later election filed with the International Bureau on:

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Kiwa Mpay Telephone No.: (41-22) 338.83.38
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# PATENT COOPERATION TREATY

# PCT

REC'D 19 SEP 2001	
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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference PD-5944-01-TMC	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/15069	International filing date (day/month/year) 31/05/2000	Priority date (day/month/year) 10/06/1999	
International Patent Classification (IPC) or national classification and IPC C07D277/20			
<p>Applicant WARNER-LAMBERT COMPANY et al.</p>			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand 09/12/2000	Date of completion of this report 17.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Usuelli, A Telephone No. +49 89 2399 7366



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**I. Basis of the report**

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):  
**Description, pages:**

1-45 as originally filed

**Claims, No.:**

1-24 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description,      pages:
- the claims,      Nos.:
- the drawings,      sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

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*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
  - the entire international application.
  - claims Nos. 4-21.

because:

- the said international application, or the said claims Nos. 4-21 (Industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
  - the written form has not been furnished or does not comply with the standard.
  - the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims 2,3,5,6,8-21,23-24
	No:	Claims 1,4,7,22
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-24
Industrial applicability (IA)	Yes:	Claims 1-3, 22-24

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No: Claims

2. Citations and explanations  
**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

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**Re Item III**

Claims 4-21 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of this claims, cf. Article 34(4)(a)(i) PCT.

**Re Item V**

1- In the present Written Opinion reference is made to the following documents:

d1: EP 0 047 109 A

d2: WO 00 18747 A

d3: US 5 523 314 A

d4: EP 0 677 517 A

d5: WO 97 26919 A

d6: DE 43 18 550 A

d7: US 5 143 929 A

d8: PATENT ABSTRACTS OF JAPAN vol. 013, no. 406 (P-930), 8 September 1989 & JP 01 147462 A

d9: PATENT ABSTRACTS OF JAPAN vol. 013, no. 406 (P-930), 8 September 1989 & JP 01 147476 A

2- Novelty

Present formula (I) is, at least in part, encompassed by formula (I) of d1 (page 2) when X1 and X2 are H, n is 1 and X is selected from phenyl substituted by (di)alkylamino or tetrahydroquinolyl. d1 discloses also a specific compound (compound 14 page 18) which fall in the ambit of present claim 1 and pharmaceutical compositions containing the compounds of formula (I). Accordingly present claims 1 and 22 are not novel in view of d1. Present formula (I) is also in part encompassed by formula (I) of d3 (column 2) when X1 and X2 are H and X is (di)alkylaminophenyl. The compounds of d3 inhibit the formation of [SPEC0803]-amyloid proteins and are thus useful for the treatment of Alzheimer disease (cf. column 31, lines 46-53). Therefore claims 1,4,7,22 are not novel vis-à-vis d3.

The compounds of the present application are novel vis-à-vis d4 and d6 on account of the group NR1R2. The compounds of formula (I) of d7 differ from the compounds of the

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present application in that they have a phenyl group bound to the amino moiety instead of a phenylalkyl group. d8 and d9 disclose ester derivatives of the compounds of the invention. d5 does not disclose any rhodanine derivative.

In view of the above considerations claims 1,4,7,22 do not fulfil the requirements of Art 33(2) PCT.

**3- Inventive Step**

3.1- Documents d3 and d4 relate to compounds which inhibit the [SPEC0803]-amyloid peptide production and are thus useful for treating various pathologic conditions such as the Alzheimer disease. Having regard to the parts of the present application rendered novel by opportune delimitation from d1 and d3, the objective technical problem can be regarded as the provision of further inhibitors of the [SPEC0803]-amyloid peptide.

3.2- Documents d3 and d4 clearly teach that 5-benzylidene substituted rhodanine derivatives inhibit the production of [SPEC0803]-amyloid peptide. In particular the compounds of d3 are identical or closely related to the compounds of the invention: the compounds of the specific examples 53, 59, and 86 differ from the present compounds of formula (I) only for the substitution pattern on the phenyl moiety.

It appears therefore that the skilled man aware of the teaching of d3 and d4 would expect that the compound of the invention could be used to solve the technical problem.

In addition d5 discloses a method of imaging amyloid deposit which involves the use of [SPEC0803]-amyloid peptide inhibitors. Therefore even the use of the compounds of formula (I) for imaging amyloid deposits is not considered to involve any inventive activity. Accordingly, claims 1-24 do not fulfil the requirements of art 33(3) PCT.

3.3- An inventive step could be acknowledged only for a subclass of the compounds of formula (I) for which is shown by means of comparative tests vis-à-vis the compounds of d3, the presence of unexpected properties. In order to be useful, the comparative tests should be made between compounds having the maximum degree of similarity. In any case an inventive step could be extended to a subclass of the products of formula (I) only if it is credibly shown that substantially all the compounds of this subclass possess unexpected properties vis-à-vis d3. This means that the possible generalisations of the results shown for specific compounds should extend only to

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those variants being obvious modifications and equivalents of the compounds tested. In the compounds tested in the present application the groups X1/ X2 represent almost always hydrogen atoms. However according to claim 1, X1 and X2 could represent, for instance, a substituted naphthylalkyl derivative. There is no basis for assuming that the claimed activity is maintained replacing a hydrogen atom by a substituted naphthylalkyl derivative. In this context it is also observed that the non-limitative definition "substituted" (without indication of the specific substituents) used in the claims has the effect of extending the breadth of the claim to an indefinite class of compounds which could never be regarded as equivalents of the compounds tested.

**4- Industrial applicability**

For the assessment of the present claims 4-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VI**

1- The priority documents pertaining to the present application were not verified at the time of establishing this first written opinion. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If later turns out that this is not correct, the P-document (d2) cited in the International Search Report could become relevant to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.

**Re Item VII**

1- The sentences "The examples...in any manner" (page 19, lines 3-5) and "It is to be...claims" (page 45, lines 7-10) are considered irrelevant and thus superfluous, cf. Rule 9.1 (iv) PCT.

2- To meet the requirements of Rule 5.1(a)(ii) PCT, the relevant background art

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disclosed in the document d4 should be identified and briefly discussed.

**Re Item VIII**

Claims 2 and 3 should be formulated as dependent claims from claim 1, Rule 6.4 PCT.